

DETAILED ACTION

This Final Office Action is responsive to the communication received 05/03/2011.

Election/Restrictions

Applicant has elected the species of the compound salmeterol BY 630/650 (see claim 92) to prosecute the invention of Group IV.

As per MPEP 803.02, the examiner will determine whether the entire scope of the claims is patentable. Applicants' elected species of compound salmeterol BY 630/650 (see the 6th compound in claim 92) appears allowable. Therefore, according to MPEP 803.02: should the elected species be found allowable, the search of the Markush-type claim will be extended. If the search is extended and a non-elected species found not allowable, the Markush-type claim shall be rejected and claims to the nonelected invention held withdrawn from further consideration. The examination of the Markush-type claims has been extended to include species: XAC - Bodipy 630/650 X (see the first compound in claim 92 09/27/2010 and drawing in the rejection below, now deleted from current claim 92 05/03/2011), which is not allowable.

Applicant has added a proviso to claim 64 that does not include XAC - Bodipy 630/650 X. If Applicant intends to exclude XAC - Bodipy 630/650 X with a proviso in claim 64, it is suggested that Applicant show the structure of XAC - Bodipy 630/650 X (e.g. see the structure of the first compound in claim 92 09/27/2010) in the proviso. The rejected species XAC - Bodipy 630/650 X meets the claim limitation of amended claim 64 because the provision requires that L be a single bond. However, as pointed out in the figure in the rejection below, L

is not a single bond in the rejected species XAC - Bodipy 630/650 X. Therefore the rejected species XAC - Bodipy 630/650 X is encompassed where L is not a single bond.

As a non-elected species has been found not allowable, the Markush-type claims have been rejected and claims to the nonelected invention held withdrawn from further consideration.

The elected embodiment, compound salmeterol BY 630/650, meets the limitations of claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131. Since the nonelected species has been found not allowable, subject matter not embraced by the elected embodiment or the above identified nonelected species is therefore withdrawn from further consideration. The limitations of the elected species in claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 are under examination. It has been determined that the entire scope claimed is not patentable.

This application contains claim(s) 47-55, 57, 59-60, 63, 69, 73-79, 83-84, 86-87 and 97-98 drawn to an invention nonelected with traverse in the reply filed on 02/20/2009. A complete reply to the rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Priority

The priority to a provisional application 60/465,807 filed 04/28/2003 was not entered because the priority claim was not filed during the time period set forth in 37 CFR 1.55(a)(1). For original applications filed under 35 U.S.C. 111(a) (other than a design application) on or after November 29, 2000, the time period is during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the

filing date of the prior application. For applications that have entered national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and the Regulations under the PCT. See 37 CFR 1.55(a)(1)(ii). If applicant desires priority under 35 U.S.C. 119(a)-(d), (f) or 365(a) based upon a prior application, applicant must file a petition for an unintentionally delayed priority claim (37 CFR 1.55(c)). The petition must be accompanied by (1) the claim (i.e., the claim required by 35 U.S.C. 119(a)-(d) and (f) and 37 CFR 1.55) for priority to the prior application, unless previously submitted; (2) a surcharge under 37 CFR 1.17(t); and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.55(a)(1) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Discussion and Answer to Argument

If Applicant desires to claim priority to provisional application 60/465,807 filed 04/28/2003 a petition must be filed as described above.

Claim Objections

Claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 is/are objected to as being drawn in-part to non-elected subject matter since the entire scope of the claims has not been examined yet. No comment on patentability can be made on claim 92 until

the entire scope of the claim has been examined; however, according to the provisions of MPEP 803.02, the examination of the instant Markush type claim has been limited to the species noted above.

Claim Rejections - 35 USC § 112 - 2nd paragraph - Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-66, 91, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by Applicant's amendatory material of "with the proviso that a) when Lig is XAC...." to claim 64.

Claim 64 is indefinite and unclear in referring to variables not recited in the claim. Clarification and/or correction is required.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
5. Secondary considerations (objective evidence of nonobviousness): a) commercial success; b) long felt need; c) evidence of unexpected results; d) skepticism of experts; and e) copying.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 64-67, 88-89, 91, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boring (1991) Bioconjugate Chemistry volume 2 pages 77 to 88 in view of Jacobson (1987) Biochemical Pharmacology volume 36 pages 1697 to 1707, Heefner (06/24/1999) PCT International Patent Application Publication WO 99/31267 A1, Jacobson (12/1987) FEBS Letters volume 225 pages 97 to 102, Jacobson (1988) Biochemical Pharmacology volume 37 pages 3653 to 3661, Sauer (1998) Bioimaging volume 6 pages 14 to 24, Cherif (04/20/2000) PCT International Patent Application Publication WO 00/22164 A1 which corresponds to English Language US Patent US 6,562,959

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B1, Burchard (01/09/2001) US Patent US 6,171,794 B1 and Buschmann (11/27/2002)

Bioconjugate Chemistry volume 14 pages 195 to 204. This rejection has been modified due to the Applicant's amendment removing XAC - Bodipy 630/650 X from claim 92 and canceling claims 95-96, 100 and 123.

XAC – BODIPY 630/650 X

The first compound listed in dependent claim 92 09/27/2010 is drawn above and named XAC - Bodipy 630/650 X. This compound meets the claims limitations of independent claim 64 as illustrated above where m = 1 and p = 0 reducing formula I to (Lig)_JL(J_TTag).

GPCR binding molecule XAC has been conjugated to multiple different molecules, including fluorescent dyes. Boring teaches XAC conjugated to the fluorescent dye fluorescein or the fluorescent dye NBD (see Abstract, page 86 left top and Table 1 compounds 5p and 5q). Jacobson 1987 Biochemical Pharmacology teaches XAC conjugated to the fluorescent dye fluorescein (see Abstract, page 1706 left bottom and Table 2 compounds 4 and 5). Heefner

teaches XAC conjugated to one of three different monochlorofluorescein fluorescent dyes or a sulfofluorescein fluorescent dye (see page 74 line 37, Table 10 Reaction 5, page 81 line 26, page 82 line 22). Jacobson 1987 FEBS Letters teaches XAC conjugated to one of thirteen different lipids (see Abstract and Table 1 compounds 16 to 28). Jacobson 1988 teaches XAC conjugated to one of 58 different molecules including peptide, diamino-, thiol-, aldehyde, and halogen substituted derivatives (see Abstract and Table 1 compounds 1 to 58).

Boring, Jacobson 1987 Biochemical Pharmacology, Heefner, Jacobson 1987 FEBS Letters and Jacobson 1988 do not explicitly teach the fluorescent dye is Bodipy 630/650 as in conjugated species XAC - Bodipy 630/650 X (structure drawn in claim 92 and above).

Multiple different biological molecules have been conjugated to the fluorescent dye Bodipy 630/650. Sauer teaches conjugating the nucleotide dUTP with the fluorescent dye Bodipy 630/650 (see Abstract and Figure 1). Cherif teaches conjugating a deoxyribo nucleotide with the fluorescent dye Bodipy 630/650 (see column 5 line 19). Burchard teaches conjugating a deoxyribo nucleotide with the fluorescent dye Bodipy 630/650 (see column 9 line 24). Buschmann teaches conjugating biotin with the fluorescent dye Bodipy 630/650 (see Abstract and Table 2).

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in arriving at the Applicant's invention as claimed with the above cited references before them. The conjugation of XAC to a fluorescent dye to generate a compound used in biological experiments is well known in the art. The conjugation of a biomolecule to the fluorescent dye Bodipy 630/650 to generate a compound used in biological

experiments is well known in the art. One of ordinary skill in the art would have recognized the interchangeability of the fluorescent dye fluorescein of Boring for the fluorescent dye Bodipy 630/650 of Sauer, Cherif, Burchard and Buschmann. The conjugated biomolecules (XAC, nucleotide dUTP, a deoxyribo nucleotide and biotin) are all small organic molecules of a similar size. The fluorescent dyes (fluorescein, NBD, monochlorofluorescein, sulfofluorescein and Bodipy 630/650)) are all small organic molecules of a similar size. Boring, Jacobson 1987 Biochemical Pharmacology, Heefner, Jacobson 1987 FEBS Letters, Jacobson 1988 teach fluorescent dyes (fluorescein, NBD, sulfofluorescein and there different monochlorofluoresceins) can be conjugated to XAC. Boring, Jacobson 1987 Biochemical Pharmacology, Jacobson 1987 FEBS Letters and Jacobson 1988 teach multiple positions including the C8 position in XAC that tolerate substitutions and retain A₁-AR binding. Boring, Jacobson 1987 Biochemical Pharmacology, Jacobson 1987 FEBS Letters, Jacobson 1988 teach a linker between XAC and a fluorescent dye wherein XAC that tolerate substitutions and retain A₁-AR binding. One of ordinary skill in the art would have recognized the interchangeability of the fluorescent dye fluorescein for the fluorescent dye Bodipy 630/650 in conjugating the fluorescent dye to the C8 position in XAC with a known linker. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Discussion and Answer to Argument

Applicant argues dependent claims 101 to 131 have not been properly considered (Reply, page 65 line 1; page 74 line 16).

The Office has demonstrated that the compound falling within the structure of the claimed genus was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The burden is on Applicant to demonstrate that the compound does not have the inherent properties of dependent claims 101 to 131.

Applicant argues that pharmacology is unpredictable (Reply, page 65 line 5).

Obvious rejections do not require absolute predictability (see MPEP 2143.02 II). While it may be true that one cannot predict the properties of any new modified compound, the references of the rejection adequately support the instantly suggested modification as described in the rejection above (e.g. Boring, Jacobson 1987 Biochemical Pharmacology, Jacobson 1987 FEBS Letters and Jacobson 1988 teach multiple positions including the C8 position in XAC that tolerate substitutions and retain A₁-AR binding. Boring, Jacobson 1987 Biochemical Pharmacology, Jacobson 1987 FEBS Letters, Jacobson 1988 teach a linker between XAC and a fluorescent dye wherein XAC that tolerate substitutions and retain A₁-AR binding.)

Applicant argues about other dyes and GPCR ligands not covered in the rejection (Reply, page 66 line 16; page 66 line 23).

These compounds have not been examined due to the species election (see Election/Restriction section above).

Applicant argues the reference individually (Reply, page 70 line 9).

The rejections are based on combinations of references.

Applicant incorrectly interprets data and argues that for XAC-Cy5 the alteration of the fluorophore to Cy5 abolishes measurable affinity (Reply, page 72 line 7).

The reference refers to the abolishment of NECA-Cy5 affinity, not the argued XAC-Cy5 affinity.

Applicant argues that one of ordinary skill in the art would only test one fluorophore, Cy5 (Reply, page 73 line 14), and that one of ordinary skill in the art would predict ahead of time which dye would work and only test one dye (Reply, page 74 line 4).

One of ordinary skill in the art would test multiple fluorophores in the course of routine experimentation to identify which fluorophore worked best.

Applicant argues that it is unexpected that some conjugated dyes do not need to be washed away after binding (Reply, page 74 line 11). Applicant is arguing the entire scope of the claim, not the species rejected.

Applicant argues it is unexpected that binding and visualization occur in the presence of unbound fluorescent ligand (Reply, page 76 line 6).

There are no facts to support the Applicant's assertion about how long it takes to bind.

Applicant argues it is unexpected that different conjugates with either dye Bodipy 630/650 or dye Texas Red have different properties (Reply, page 76 line 12).

It is not unexpected that different fluorophores have different properties.

Applicant argues it is unexpected that a black dye quenches signals (Reply, page 77 line 1).

It is not unexpected that black dyes quench fluorescing signals.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64-67, 88-89, 91-92, 99, 101-104, 107, 109-114, 118, 120, 122 and 125-131 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-24 of copending Application No. 11/576,035.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a fluorescently tagged nucleoside ligand for adenosine A1 and other G protein coupled receptors. The claims of the copending Application 11/576,035 are drawn to an assay using a fluorescently tagged nucleoside ligand for adenosine A1 and other G protein coupled receptors.

Therefore the present claims are obvious in view of the claims of the copending Application 11/576,035.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion and Answer to Argument

Applicants requested the ODP rejection be held in abeyance. Applicants have not provided any specific traversal over the above ODP rejection. Thus, the above rejection is maintained for the reasons of record.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and

provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported *in ipsius verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The Examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian Boesen/
Examiner, Art Unit 1636

/Ardin Marschel/
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